REMARKS

Claims 1-83 were previously submitted for examination. Claims 1-9 and 60-80 were withdrawn from consideration, and claims 19-21 and 40-57 have been canceled. Claims 81-96 were previously added. Therefore claims 10-18, 22-39, 58, 59 and 81-96 are currently pending.

Rejections under 35 U.S.C. § 102

Claims 10-18, 22, 24-30, 58, 59, 82-87, 89-91, 93, 94 and 96 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Colford et al. (Endocrine Society 79th Meeting Abstract (1997) p3-194; applicant submitted IDS information filed 1/13/2006 #57) (Colford).

Colford is alleged to teach polyclonal antibody directed to N-terminal PTH_{1-7}. The Examiner states that Colford's PTH_{1-7} antibody binds to the N-terminal amino acids 1-7 of PTH. Colford is also alleged to teach that the PTH_{1-7} [antibody] is used in an assay for measuring the whole PTH in a sample. Colford allegedly compares well-known commercial assay kits and determined the presence of one or two immunoreactive PTH species (fragments) in addition to intact PTH, and the PTH_{1-7} antibody binds only to the intact PTH (showed only one peak). The Examiner alleges that the assay using Colford PTH_{1-7} antibody does not bind to the non-whole PTH fragment in the sample (*citing* Abstract; page IMU 3288, 3289 and 3297).

With respect to the feature of "detecting said whole PTH at a physiological level in said mammalian sample," the Examiner cites MPEP §2112 that states "[Where] the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established." In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCP A 1977) (emphasis added). According to the Examiner, since the antibody disclosed by Colford et al. can detect whole PTH in hyperparathyroidism patient's serum as recited in the instant claims, it is inherent that antibodies from Colford et al. can also measure PTH at physiological levels.

With respect to claims 11-12, 14, 15, 88, 93 and 94, Colford is alleged to teach detecting PTH levels from human PTH dysfunction patients.

With respect to claims 17, 18, 85, 87, 89 and 96, the Examiner states that the instant claims recite the antibody recognizing either human PTH $_{1\text{-}5}$, human PTH $_{1\text{-}6}$ or human PTH $_{1\text{-}8}$. The Examiner alleges that such features are within the scope of the Colford's teachings. According to the Examiner, Colford teaches polyclonal antibody directed to N-terminal $PTH_{1\text{-}7}$. The Examiner further alleges that since epitopes are around 4-7 amino acids residues, therefore human PTH $_{1\text{-}5}$, $_{1\text{-}6}$ or $_{1\text{-}8}$ [antibodies] are within the scope of Colford's teachings.

With respect to claims 22, Colford is alleged to teach that the non-whole PTH is a fragment of PTH $_{34\text{-}84}$.

Applicant respectfully traverses this rejection because Colford does not disclose each and every limitation of claims 10-18, 22, 24-30, 58, 59, 82-87, 89-91, 93, 94 and 96 of the present application.

Colford "PTH (1-7) antibody" does not specifically bind to an N-terminal sequence of whole PTH

Colford refers to a PTH (1-7) antibody and the use of the PTH (1-7) antibody in testing various PTH forms after HPLC separation. Colford does not provide any information as to how the PTH (1-7) antibody was generated, characterized, and/or purified, if it was purified at all.

In any case, Colford's own data demonstrate that Colford "PTH (1-7) antibody" is not specific for any epitope within N-terminal sequence of whole PTH at all, *e.g.*, $PTH_{1\text{-}5}$, $PTH_{1\text{-}6}$, $PTH_{1\text{-}7}$, $PTH_{1\text{-}8}$, $PTH_{1\text{-}9}$, $PTH_{1\text{-}10}$, $PTH_{1\text{-}11}$, $PTH_{1\text{-}12}$, $PTH_{1\text{-}13}$, $PTH_{1\text{-}14}$ or $PTH_{1\text{-}15}$. If the Colford "PTH (1-7) antibody," as alleged by the Examiner, were specific for an epitope within N-terminal sequence of whole PTH, the Colford "PTH (1-7) antibody" would be able to distinguish whole PTH from an interfering non-(1-84) PTH fragment, *e.g.*, PTH (7–84). As shown in detail below,

Colford's own experiments demonstrate that its "PTH (1-7) antibody" is incapable of distinguishing whole PTH from an interfering non-(1-84) PTH fragment.

According to the presentation material of Colford 1997 Abstract (Colford 1997 Presentation) (Ex. I of Scantibodies' '566 patent reexamination request (90/007,685) (Exhibit 1)), three peaks containing PTH, PTHα peak, PTHβ peak and PTHγ peak, were detected by the Nichols Allegro™ intact PTH test in various HPLC fractions. (Ex. I of 90/007,685, Colford 1997 Presentation at page IMU-3288 (Exhibit 1).) An immunoassay using the PTH (1-7) antibody referred to in Colford detected the forms of PTH contained in the PTHα peak and, to a lesser degree, the forms of PTH contained in the PTHβ peak. (*Id.*) According to the Colford 1997 Presentation, PTHα peak contains the unfragmented whole PTH (1-84 PTH) and PTHβ and PTHγ contain unspecified N-terminal PTH fragments (*Id.* at page IMU-3289.) The immunoassay using the PTH (1-7) antibody referred to in Colford had meaningful cross-reactivity for PTHβ (*i.e.*, the PTH (1-7) antibody measured certain amount of the PTH forms contained in the PTHβ peak compared to the percent measured by the Nichols Allegro IRMA intact PTH assay).

Both the 1997 Colford Abstract (Ex. A of Scantibodies' '566 patent reexamination request (90/007,685) (Exhibit 2)) and the Presentation material of Colford 1997 Abstract (Colford 1997 Presentation) (Ex. I of 90/007,685) (Exhibit 1) refer to a "PTH (1-7) antibody." (Ex. A at page IMU-3281 (Exhibit 2) and Ex. I at pages IMU-3283, IMU-3284 and IMU-3288 (Exhibit 1).) The poster from the 1996 Annual Meeting of the Endocrine Society, San Francisco, CA, U.S.A., Todd Jensen, Jon Spring, and John Colford, entitled "COMPARING SPECIFICITY FOR INTACT HUMAN PARATHYROID HORMONE BETWEEN INCSTAR PTH SP AND NICHOLS INTACT PTH ASSAYS" (Jensen 1996 Poster) (Ex. J of 90/007,685) (Exhibit 3) refers to "EXP (1-7)." (Ex. J at pages 4, 5 and 9 (Exhibit 3).) According to Colford, The "EXP (1-7)" in the Jensen 1996 Poster refers to an immunoassay for PTH in which the "PTH (1-7) antibody" referred to in the Colford Abstract and the Colford 1997 Presentation was used (*i.e.*, the antibody used in the EXP (1-7) assay and the PTH (1-7) assay are one and the same). (Ex. K of 90/007,685, Declaration of John Colford (Exhibit 4).)

As shown in Jensen 1996 Poster, in many instances, the immunoassay using the "PTH (1-7) antibody" gave higher or comparable PTH test results from the PTH test results obtained using Nichols Allegro™ IRMA Intact PTH test. (Ex. J of 90/007,685, Jensen 1996 Poster at page 9 (Exhibit 3).) It is known in the art that Nichols Allegro™ IRMA Intact PTH test cannot distinguish a whole PTH from an interfering non-(1-84) PTH fragment, *e.g.*, PTH 7-84 fragment. As demonstrated in Gao et al., *J. Bone Miner. Res.*, 16(4):605-14 (2001):

> Assay specificity to synthetic PTH (7-84) was studied by comparing this whole PTH IRMA [developed by Scantibodies Laboratories, Inc.] with Nichols intact PTH IRMA. Nearly 100% cross-reaction to this fragment was observed with Nichols intact PTH assay, but no cross-reaction was detected with this newly developed whole PTH IRMA even at a PTH (7-84) concentration of 10,000 pg/ml (Fig. 2).

(*See* Ex. L of 90/007,685, Gao et al., *J. Bone Miner. Res.*, 16(4):605-14 (2001), Figure 2, at page 608 (Exhibit 5).) Accordingly, the higher or comparable PTH test results from the immunoassay using the "PTH (1-7) antibody" indicate that Colford's PTH assay cannot distinguish a whole PTH from a N-terminal PTH fragment. The inability of the immunoassay using Colford "PTH (1-7) antibody" to distinguish whole PTH from an interfering non-(1-84) PTH fragment demonstrates that Colford "PTH (1-7) antibody" is not specific for any epitope within N-terminal sequence of whole PTH at all, *e.g.*, PTH_{1-5}, PTH_{1-6}, PTH_{1-7}, PTH_{1-8}, PTH_{1-9}, PTH_{1-10}, PTH_{1-11}, PTH_{1-12}, PTH_{1-13}, PTH_{1-14} or PTH_{1-15}.

Colford lacks the limitation "avoids binding to a non-whole PTH fragment in said sample"

In addition, claims 10-18, 22, 24-30, 58, 59, 82-87, 89-91, 93, 94 and 96 also require the claimed "said isolated antibody avoids binding to a non-whole PTH fragment in said sample." As discussed above, Colford "PTH (1-7) antibody" binds to interfering non-(1-84) parathyroid hormone fragment because the immunoassay using Colford "PTH (1-7) antibody" is incapable of distinguishing whole PTH from an interfering non-(1-84) PTH fragment.

Colford does not inherently disclose the presently claimed invention

As discussed above, the binding specificity of Colford "PTH (1-7) antibody" and the antibodies used in the presently claimed methods and kits are significantly different. These differences indicate that that Colford "PTH (1-7) antibody" and the antibodies used in the presently claimed methods and kits are not identical or substantially identical, as alleged by the Examiner. In addition, Colford does not provide for any information as to how the PTH (1-7) antibody was generated, characterized, and/or purified, if it was purified at all. Nothing in Colford indicates that the identical or substantially identical processes were used in generating and/or isolating Colford "PTH (1-7) antibody" and the antibodies used in the presently claimed methods and kits. Therefore, the Examiner has not provided for sufficient evidence to show that Colford inherently anticipates the presently claimed methods and kits.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the anticipation rejection of claims 10-18, 22, 24-30, 58, 59, 82-87, 89-91, 93, 94 and 96 over Colford.

Rejections under 35 U.S.C. § 103

Claims 23 and 88

Claims 23 and 88 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Colford et at. in view of Lepage et al. (Clinical Chemistry 1998 Vol. 44, page 805) (Lepage).

Colford is discussed above and is alleged to teach that a non-whole PTH_{34-84} has been used to detect the non-whole PTH. The Examiner acknowledges that Colford does not explicitly teach using a PTH fragment 7-84 to detect the non-whole PTH level. Lepage is alleged to teach a non-whole PTH_{7-84} circulating in the blood interfering with the measuring of the whole PTH level (See Abstract). Nevertheless, the Examiner alleges that it would have been obvious to one ordinary skill in the art at the time the invention was made to have provide Colford with the non-whole PTH

7-84 as taught by Lepage in order to measure the true whole PTH levels not interfering with the non-whole PTH.

Applicant respectfully traverses this rejection and submits that Colford in view of Lepage does not render obvious 23 and 88 of the present application.

First, neither Colford nor Lepage provides for the requisite motivation to combine the two references. Claims 23 and 88 depend on claims 10 and 87, respectively, which are directed to methods for measuring a physiological level of whole parathyroid hormone in a mammalian sample. Both Colford nor Lepage are directed to studies on PTH fragments, and are not directed to methods for measuring a physiological level of whole parathyroid hormone in a mammalian sample. For their intended purpose, *i.e.*, studies on PTH fragments, both Colford and Lepage succeeded in isolating some PTH fragments and characterizing the PTH fragments to a certain degree. Therefore, skilled artisans would not see any need to modify or combine the two references.

In addition, both references use similar methodology, *i.e.*, using HPLC to separate the PTH fragments and using immunoassay to characterize the PTH fragments. Therefore, skilled artisans would not see any benefit from combing the references.

Further, claims 23 and 88 require the use of an anti-PTH antibody that "avoids binding to a non-whole PTH fragment" in a sample to be tested and the anti-PTH antibody "specifically binds to an epitope comprised in PTH_{1-5}, PTH_{1-6}, PTH_{1-7}, PTH_{1-8}, PTH_{1-9}, PTH_{1-10}, PTH_{1-11}, PTH_{1-12}, PTH_{1-13}, PTH_{1-14} or PTH_{1-15}." In other words, claims 23 and 88 are directed to immunoassays for measuring a physiological level of whole parathyroid hormone in a mammalian sample. In contrast, both Colford and Lepage are directed to studies on PTH fragments that are based on HPLC separation of the PTH fragments. It is a well established rule that if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP § 2143.01V. *citing In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Accordingly, skilled artisans would not be motivated to modify or combine Colford and Lepage, which intend to study PTH fragments, to

arrive at the methods of claims 23 and 88, which specifically "avoids binding to a non-whole PTH fragment," because such a modification or combination, as suggested by the Examiner, would defeat the purpose of Colford and Lepage.

Similarly, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. MPEP § 2143.01VI. *citing In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Both Colford and Lepage are directed to studies on PTH fragments that are based on HPLC separation of the PTH fragments. In contrast, claims 23 and 88 are directed to immunoassays for measuring a physiological level of whole parathyroid hormone in a mammalian sample, and the use of HPLC is not required in the methods of claims 23 and 88. Accordingly, skilled artisans would not be motivated to modify or combine Colford and Lepage, which requires the use of HPLC separation of PTH fragments, to arrive at the methods of claims 23 and 88, which do not require the use of HPLC separation of PTH fragments," because such a modification or combination, as suggested by the Examiner, would change the principle of operation of Colford and Lepage.

Even assuming, *arguendo*, that there were motivation to combine Colford and Lepage, the combination of the two references does not teach all elements of claims 23 and 88. Claims 23 and 88 require the use of an anti-PTH antibody that "avoids binding to a non-whole PTH fragment" in a sample to be tested and the anti-PTH antibody "specifically binds to an epitope comprised in PTH_{1-5}, PTH_{1-6}, PTH_{1-7}, PTH_{1-8}, PTH_{1-9}, PTH_{1-10}, PTH_{1-11}, PTH_{1-12}, PTH_{1-13}, PTH_{1-14} or PTH_{1-15}." As discussed above in connection with the anticipation analysis, Colford does not teach these elements because the immunoassay using Colford "PTH (1-7) antibody" is incapable of distinguishing whole PTH from an interfering non-(1-84) PTH fragment. Colford's deficiency is not cured by Lepage because Lepage uses HPLC, not immunoassay, to detect whole PTH.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection of claims 23 and 88 over Colford in view of Lepage.

Claims 31-39, 81 and 84

Claims 31-39, 81 and 84 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Colford.

The Examiner acknowledges that Colford does not explicitly teach measuring the physiological levels of PTH less than 4 pmole/L or from 7 picogram/ml to 39 picogram/ml. Nevertheless, the Examiner alleges that it would have been obvious to one having ordinary skill in the art at the time the invention was made to optimize the effectiveness from the selection of antibody clones, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. With respect to claims 33, 35 and 38, Colford is alleged to teach measuring the ratios of whole PTH versus total (intact) PTH levels.

Applicant respectfully traverses this rejection and submits that Colford does not render obvious claims 31-39, 81 and 84 of the present application. Claims 31-39, 81 and 84 all depend on claim 10 directly or indirectly. Colford does not render obvious claims 31-39, 81 and 84 for the same or similar reasons that Colford in view of Lepage does not render obvious 23 and 88 of the present application.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection of claims 31-39, 81 and 84 over Colford.

Claims 92 and 95

Claims 92 and 95 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Colford et al. in view of Rucinski et at. (Calcified Tissue International 1995 Vol. 56, page 83) (Rucinski). Colford is alleged to teach detecting PTH levels in human serum samples. The Examiner acknowledges that Colford does not explicitly teach detecting rat or goat samples. Rucinski is alleged to teach measuring rat and goat PTH levels by immunoassay methodology. The Examiner alleges that it would have been obvious to one ordinary skill in the art at the time the

invention was made to have provided Colford with the alternative mammals, such as rat or goat as taught by Rucinski since using alternative non-human mammals, such as rat or goat model is widely accepted and practiced in the field for better assessment of subsequent clinical significance on human.

Applicant respectfully traverses this rejection and submits that Colford in view of Rucinski does not render obvious claims 92 and 95 of the present application. Claims 92 and 95 both depend on claim 10 directly or indirectly. Colford does not render obvious claims 92 and 95 for the same or similar reasons that Colford in view of Lepage does not render obvious 23 and 88 of the present application.

In addition, claim 92 depends on claim 91, which requires that the anti-PTH antibody is "produced by immunizing a mammal with whole PTH, collecting the antibody from the mammal and isolating the antibody by binding the antibody to an epitope comprised in PTH_{1-5}, PTH_{1-6}, PTH_{1-7}, PTH_{1-8}, PTH_{1-9}, PTH_{1-10}, PTH_{1-11}, PTH_{1-12}, PTH_{1-13}, PTH_{1-14} or PTH_{1-15}." Colford does not provide any information as to how its "PTH (1-7) antibody" was generated, characterized, and/or purified, if it was purified at all. Rucinski does not cure the defect of Colford because the anti-PTH antibody used in Rucinski is affinity purified with rat PTH_{1-34} fragment (Rucinski at page 83, right column). Further, claim 92 is directed to a method for measuring a physiological level of whole parathyroid hormone in a goat sample. Colford does not teach an immunoassay for PTH in a goat sample. Rucinski does not cure the defect of Colford because teaches an immunoassay for PTH in a rat, but goat, sample.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection of claims 92 and 95 over Colford in view of Rucinski.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 53221-2000623. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 2, 2006

Respectfully submitted,

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